

سبحان الله العظيم






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# **Genetics of Common Disorders with Complex Inheritance**

Diseases such as congenital birth defects, myocardial infarction, cancer, mental illness, diabetes, and Alzheimer disease cause morbidity and premature mortality in nearly two of every three individuals during their lifetimes



# Many of these diseases

- run in families .
- in the relatives of affected individuals more frequently than in the general population .
- their inheritance generally does not follow one of the mendelian patterns seen in the single-gene disorders .

## multifactorial (or complex) inheritance pattern

- to result from complex *interactions* between a number of genetic and environmental factors.
- family members share a greater proportion of their genetic information and environmental exposures than do individuals chosen at random in the population.

## gene-gene **and** gene-environment interactions

- relatives of an affected individual are more likely to experience the same **gene-gene** and **gene-environment interactions** that led to disease in the proband in the first place than are individuals who are unrelated to the proband .

# polygenic **or** multigenic **effects**

- represents an interaction between the collective effect of the genotype at one or, more commonly, multiple loci either to raise or to lower susceptibility to disease, combined with a variety of environmental exposures that may trigger, accelerate, exacerbate, or protect against the disease process.



## Categories of the complex phenotypes of multifactorial disorders

- **1-qualitative:** genetic disease that is either present or absent
- **2-quantitative** :measurable physiological or biochemical quantities such as height, blood pressure, serum cholesterol concentration, and body mass index (a measure of obesity) that underlie many common and devastating illnesses in the population.

# familial aggregation

- affected individuals may cluster in families.
- The converse, however, is not necessarily true: familial aggregation of a disease does not mean that a disease must have a genetic contribution .
- Family members may develop the same disease or trait by chance alone, particularly if it is a common one in the population. Even if familial aggregation is not due to chance, families share more than their genes; for example, they often have cultural attitudes and behaviors, socioeconomic status, diet, and environmental exposures in common.

- It is the task of the genetic epidemiologist to determine whether familial aggregation is coincidental or the result of factors common to members of the family and to assess the extent to which those common factors
- Ultimately, gene mapping studies to locate and identify the particular loci and alleles involved provide the definitive proof of a genetic contribution to multifactorial disease

# concordant **for the disease**

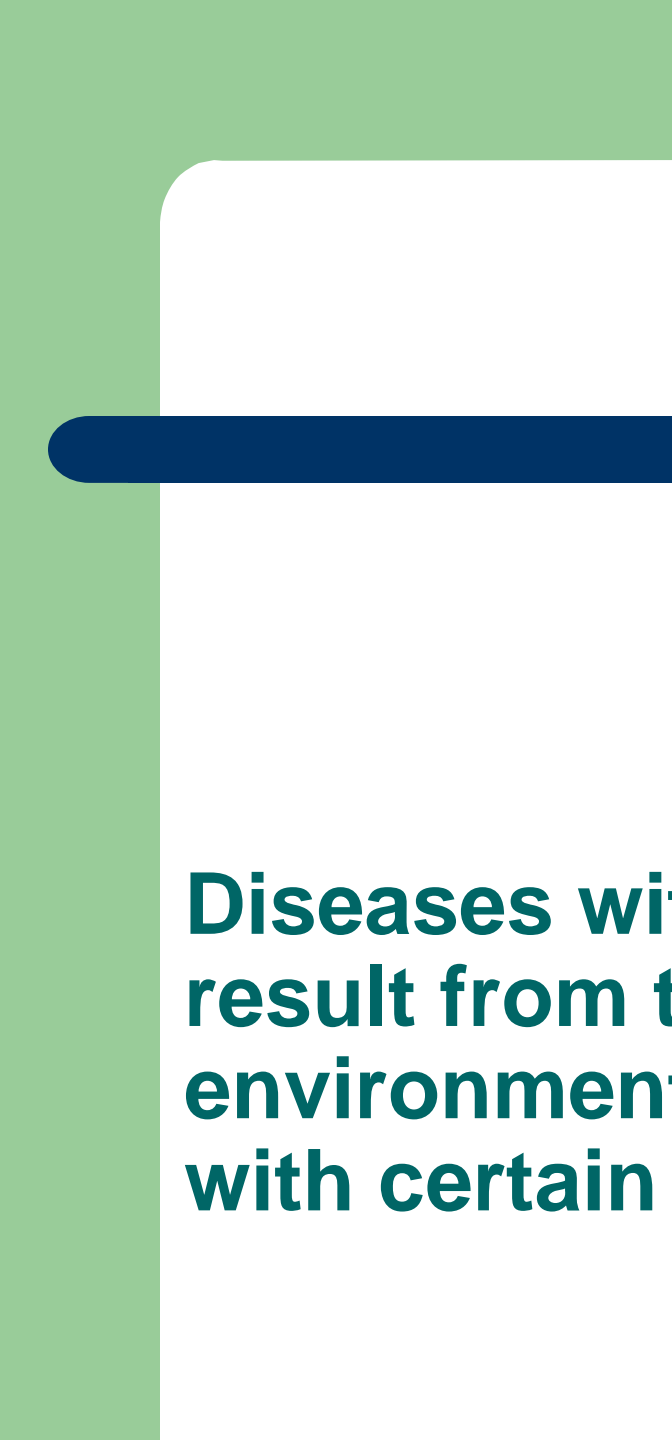
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- When two related individuals in a family have the same disease



## discordant **for the disease**

- when only one member of the pair of relatives is affected and the other is not, the relatives



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**Diseases with complex inheritance  
result from the impact of  
environmental factors on individuals  
with certain genotypes**

- Discordance for phenotype between relatives who share a genotype at loci that predispose to disease can be explained if the unaffected individual has not experienced the other factors (environmental or chance occurrences) necessary to trigger the disease process and make it manifest. Conversely, concordance for a phenotype may occur even when the two affected relatives have different predisposing genotypes, if the disease in one relative is a **genocopy** or **phenocopy** of the disease in the other relative.

# genocopy

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- A genotype that determines a phenotype closely similar to that determined by a different genotype.



# phenocopy

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- A mimic of a phenotype that is usually determined by a specific genotype, produced instead by the interaction of some environmental factor with a normal genotype.

## Measuring Familial Aggregation in Qualitative Traits *Relative Risk $\lambda_r$*

$$\lambda_r = \frac{\text{Prevalence of the disease in the relatives of an affected person}}{\text{Prevalence of the disease in the general population}}$$

- The subscript  $r$  for  $\lambda$  is used here to refer to relatives; in practice, one measures  $\lambda$  for a particular class of relatives, e.g.,  $r = s$  for sibs,  $r = p$  for parents .
- The population prevalence enters into the calculation because the more common a disease is, the greater is the likelihood that aggregation may be just a coincidence rather than a result of sharing the alleles that predispose to disease.

$$\lambda_r = 1$$

- indicates that a relative is no more likely to develop the disease than is any individual in the population.



## *Case-Control Studies*

- Another approach to assessing familial aggregation is the case-control study, in which patients with a disease (the cases) are compared with suitably chosen individuals without the disease (the controls), with respect to family history of disease (as well as other factors, such as environmental exposures, occupation, geographical location, parity, and previous illnesses).

## positive family history

- the frequency with which the disease is found in the extended families of the cases is compared with the frequency of positive family history among suitable controls, matched for age and ethnicity, but who do not have the disease

# multiple sclerosis (MS)

- approximately 3.5% of siblings of patients with MS also had MS .
- among the relatives of matched controls without MS (0.2%) .

# Bias

- **ascertainment bias** :a difference in the likelihood that affected relatives of the cases will be reported to the epidemiologist as compared with the affected relatives of controls.
- **recall bias** :A proband's relatives may be more likely than a control's relatives to know of other family members with the same or similar disease or may be more motivated to respond to questioning because of familiarity with the disease .

**Finally, an association found in a case-control study does not prove causation.**

- If two factors are not independent of each other, such as ethnic background and dietary consumption of certain foods, a case-control study may find a significant association between the disease and ethnic background when it is actually the dietary habits associated with ethnic background that are responsible

## For example

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- the lower frequency of coronary artery disease among Japanese compared with North Americans becomes less pronounced in first-generation Japanese who emigrated to North America and adopted the dietary customs of their new home.

# Concordance and Allele Sharing Among Relatives

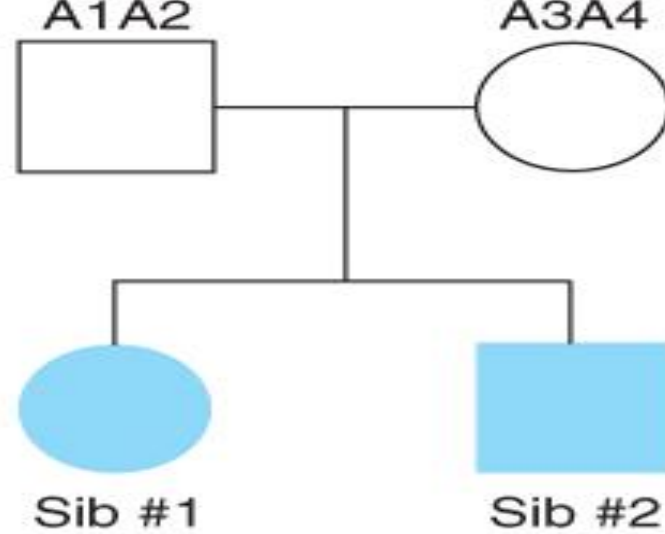
- The more closely related two individuals are in a family, the more alleles they have in common, inherited from their common ancestors.
- Conversely, the more distantly related the relative is to the proband, the fewer the alleles shared between the proband and the relative

The child has one allele in common with each parent at every locus, that is, the allele the child inherited from that parent.

- A pair of sibs inherits the same two alleles at a locus 25% of the time, no alleles in common 25% of the time, and one allele in common 50% of the time .

$$0.25 (2 \text{ alleles}) + 0.5 (1 \text{ allele}) + 0.25 (0 \text{ alleles}) \\ = 1 \text{ allele}$$





Genotype of sib #1

	A1A3	A1A4	A2A3	A2A4
Genotype of sib #2				
A1A3	2	1	1	0
A1A4	1	2	0	1
A2A3	1	0	2	1
A2A4	0	1	1	2

- Relationship to Proband Proportion of Alleles in Common with Proband Monozygotic twin 1, First-degree relative  $1/2$ , Second-degree relative  $1/4$ , Third-degree relative  $1/8$ .

- The more closely related two individuals are, the more likely they are to share home environment as well as genes. One way to separate family environment from genetic influence is to compare the incidence of disease in unrelated family members (adoptees, spouses) with that in biological relatives.

# Twin Studies

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- Another common method for separating genetic from environmental influences on disease is to study twins, both monozygotic (MZ) and dizygotic (DZ).

# Monozygotic twins

- arise from the cleavage of a single fertilized zygote into two separate zygotes early in embryogenesis.
- As a result, MZ twins have identical genotypes at every locus and are always of the same sex.

# Dizygotic twins

- arise from the simultaneous fertilization of two eggs by two sperm .
- DZ twins are siblings who share a womb and, like all siblings, share, on average, 50% of the alleles at all loci.
- DZ twins are of the same sex half the time and of opposite sex the other half.

# ***Disease Concordance in Monozygotic Twins***

- An examination of how frequently MZ twins are concordant for a disease is a powerful method for determining whether genotype alone is sufficient to produce a particular disease .

# Example

- one MZ twin has sickle cell disease, the other twin will also have sickle cell disease.
- one MZ twin has type 1 diabetes mellitus (previously known as insulin-dependent or juvenile diabetes), only about 40% of the other twins will also have type 1 diabetes.  
*Disease concordance less than 100% in MZ twins is strong evidence that nongenetic factors play a role in the disease.*





			Concordance (%)
Disorder		MZ	DZ
Nontraumatic epilepsy		70	6
Mental retardation		17.8	2
Type 1 diabetes		40	4.8
Schizophrenia		46	15
Bipolar disease		62	8
Osteoarthritis		32	16
Rheumatoid arthritis		12.3	3.5
Psoriasis		72	15
Cleft lip with or without cleft palate		30	2
Cleft palate with or without cleft lip		66	6

## *Limitations of Twin Studies*

- First, MZ twins do not have precisely identical genes or gene expression despite starting out with identical genotypes at the time the zygote cleaves in two to create the MZ twins.

## example

- somatic rearrangements in the immunoglobulin and T-cell receptor loci will differ between MZ twins in various lymphocyte subsets . In addition, on the X chromosome, random X inactivation after cleavage into two female MZ zygotes produces significant differences in the expression of alleles of X-linked genes in different tissues .

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- Second, environmental exposures may not be the same for twins, especially once the twins reach adulthood and leave their childhood home.
  - Even intrauterine environment may not be the same .

## example

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- MZ twins frequently share a placenta, and there may be a disparity between the twins in blood supply, intrauterine development, and birth weight.

- Third, measurements of disease concordance in MZ twins give an average estimate that may not be accurate if the relevant predisposing alleles or environmental factors are different in different twin pairs.

## example

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- the disease may not always be genetic in origin, that is, nongenetic phenocopies may exist.

# Finally,

- ascertainment bias
- **volunteer-based ascertainment**  
:particularly when one twin with a particular disease is asked to recruit the other twin to participate in a study .
- **population-based ascertainment** :if they are ascertained first as twins and only then is their health status examined



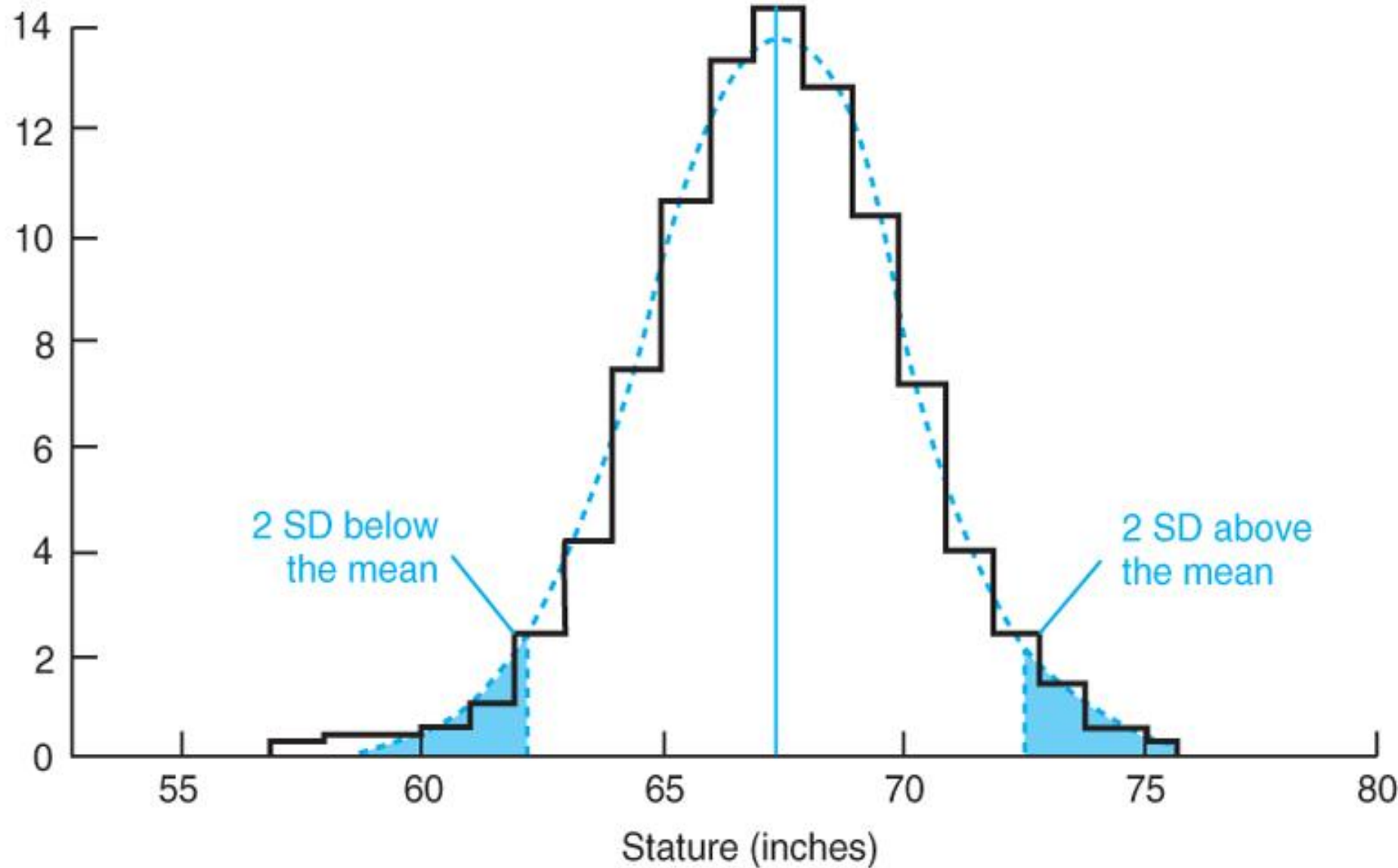
# Genetic Analysis of Quantitative Traits

- Measurable physiological quantities, such as blood pressure, serum cholesterol concentration, and body mass index, vary among different individuals and are important determinants of health and disease in the population.

# The Normal Distribution

- As is often the case with physiological quantities measured in a population, a graph of the number of individuals in the population (y-axis) having a particular quantitative value (x-axis) produces the familiar bell-shaped curve known as the **normal (gaussian) distribution** .

Number of men (thousands)



# Quantitative phenotype

- . Any physiological quantity that can be measured .

# Total phenotypic variance

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- The variance of a measured quantity in the population .

# The Normal Range

- The concept of the normal range of a physiological quantity is fundamental to clinical medicine.

# How is the "normal" range determined?

- In many situations in medicine, a particular measured physiological value is "normal" or "abnormal" depending on how far it is above or below the mean.

# Familial Aggregation of Quantitative Traits

- Quantitative traits, however, are not either present or absent; they are measurements.
- Just as familial aggregation, as measured by  $\lambda_r$  and case-control studies, is used to assess the role of heredity in qualitative disease traits, family studies can also be used to determine the role of heredity in quantitative traits.



# coefficient of correlation ( $r$ )

- is a statistical measure applied to a pair of measurements, such as, for example, a person's blood pressure and the mean blood pressures of that person's siblings .

# positive correlation

- exists between the blood pressure measurements in a group of patients and the blood pressure measurements of their relatives if it is found that the higher a patient's blood pressure, the higher are the blood pressures of the patient's relatives.

# negative correlation

- exists when the greater the increase in the patient's measurement, the lower the measurement is in the patient's relatives.
- Note: The measurements are still correlated, but in the opposite direction .

# Heritability ( $h^2$ )

- is defined as the fraction of the total phenotypic variance of a quantitative trait that is caused by genes and is therefore a measure of the extent to which different alleles at various loci are responsible for the variability in a given quantitative trait seen across a population.

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- The higher the heritability, the greater is the contribution of genetic differences among people in causing variability of the trait .
- The value of  $h^2$  varies from 0, if genes contribute nothing to the total phenotypic variance, to 1, if genes are totally responsible for the phenotypic variance.

# practical difficulties

- One is that relatives share more than their genes; they also share environmental exposures, and so the correlation between relatives may not reflect simply their familial genetic relationship.
- Second, even when the heritability of a trait is high, it does not reveal the underlying mechanism of inheritance of the trait, such as the number of loci involved or how the various alleles at those loci interact .

- Finally, as tempting as it is to think of heritability as an intrinsic quality of a particular quantitative trait, it cannot be considered in isolation from the population group and living conditions in which the estimate is being made.



## *Estimating Heritability from Twin Studies*

$$h^2 = \frac{\text{Variance in DZ pairs} - \text{Variance in MZ pairs}}{\text{Variance in DZ pairs}}$$

# Interpretation

- If the variability of the trait is determined chiefly by environment, the variance within pairs of DZ twins will be similar to that seen within pairs of MZ twins, and the numerator, and therefore  $h^2$  itself, will approach 0. If the variability is determined exclusively by genetic makeup, variance of MZ pairs is zero, and  $h^2$  is 1.

# Characteristics of Inheritance of Complex Diseases

- Genes contribute to diseases with complex inheritance, but these diseases are not single-gene disorders and do not demonstrate a simple mendelian pattern of inheritance.
- Diseases with complex inheritance often demonstrate familial aggregation because relatives of an affected individual are more likely to have disease-predisposing alleles in common with the affected person than are unrelated individuals.
- Pairs of relatives who share disease-predisposing genotypes at relevant loci may still be discordant for phenotype (show lack of penetrance) because of the crucial role of nongenetic factors in disease causation. The most extreme examples of lack of penetrance despite identical genotypes are discordant monozygotic twins.
- The disease is more common among the close relatives of the proband and becomes less common in relatives who are less closely related and therefore share fewer predisposing alleles. Greater concordance for disease is expected among monozygotic versus dizygotic twins.

# genetic epidemiology

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- Empirical studies designed to identify how particular alleles at specific loci interact with relevant environmental factors to alter susceptibility to complex disease .

# Digenic Retinitis Pigmentosa

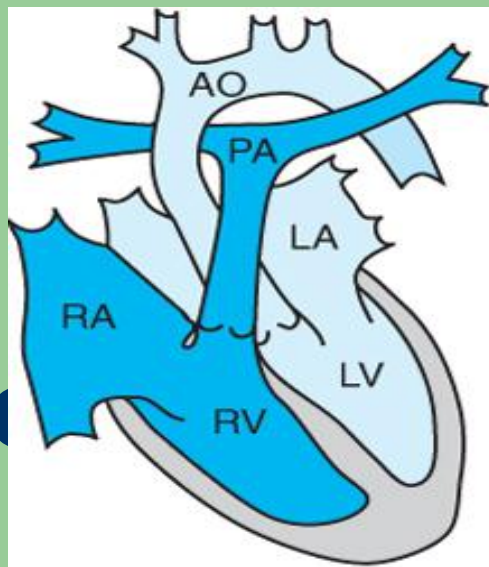
- a form of retinal degeneration .
- Two rare mutations in two different unlinked genes encoding proteins found in the photoreceptor.
- However, patients heterozygous for *both* mutations *do* develop the disease.

- this disease is caused by the simplest form of multigenic inheritance, inheritance due to the effect of mutant alleles at two loci without any known environmental factors that influence disease occurrence or severity .

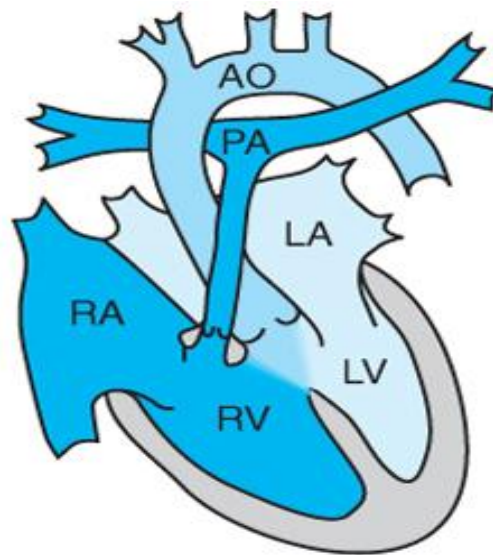
- in patients with digenic retinitis pigmentosa, the deleterious effect of each mutation alone is insufficient to cause disease, but their joint presence is sufficient to cross a threshold of cell damage, photoreceptor death, and loss of vision.

# Congenital Heart Defects

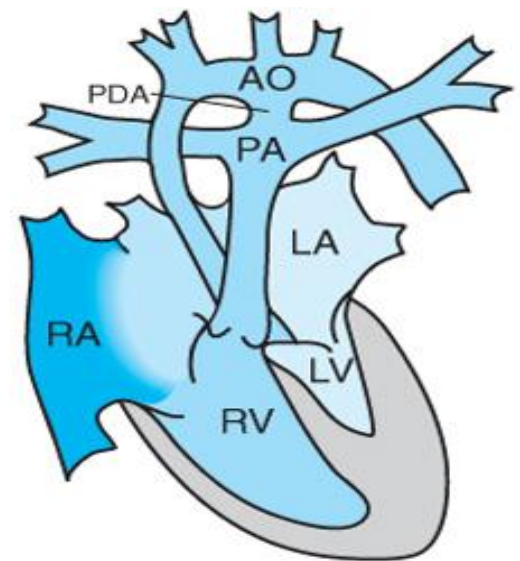
- Congenital heart defects (CHDs) are common, with a frequency of about 4 to 8 per 1000 births. They are a heterogeneous group, caused in some cases by single-gene or chromosomal mechanisms and in others by exposure to teratogens, such as rubella infection or maternal diabetes. The cause is usually unknown, and the majority of cases are believed to be multifactorial in origin.



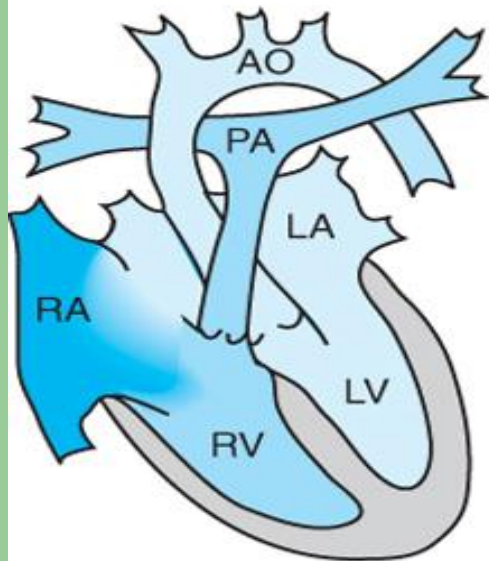
Normal



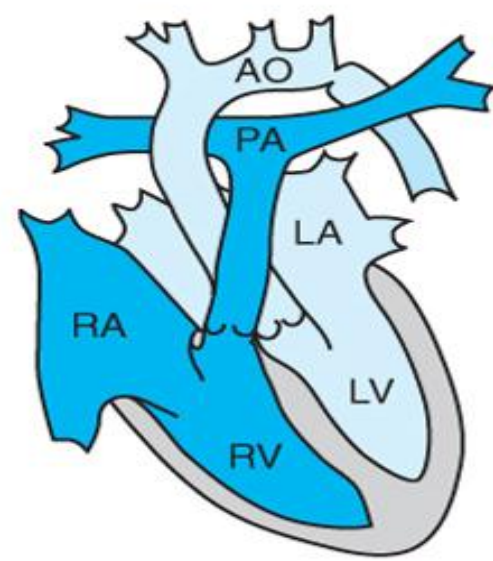
Tetralogy of Fallot



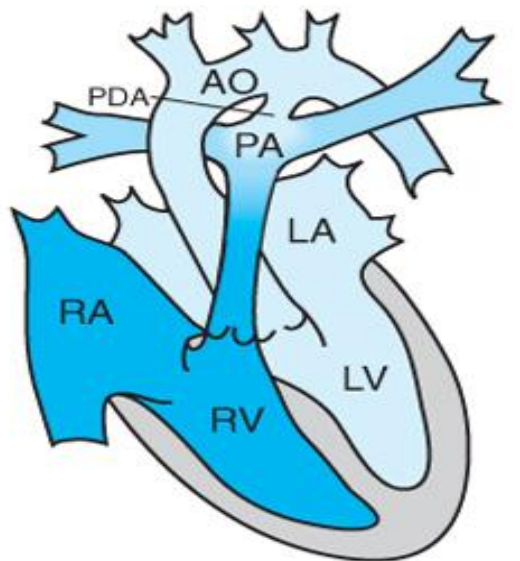
Hypoplastic left heart



Atrial septal defect



Coarctation of the aorta



Patent ductus arteriosus (PDA)



Defect	Population Incidence (%)	Frequency in Sibs (%)	$\lambda_{sib}$
Septal defect	0.17	4.9	25
Patent ductus arteriosus	0.083	3.2	38
Atrial septal defect	0.066	3.2	48
Aortic stenosis	0.044	2.6	59